Review Article

Gene polymorphism-related differences in the outcomes of abiraterone for prostate cancer: a systematic overview

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Abstract: Numerous prostate cancer (PC) associated genes have been reported in previous genome-wide association studies. Elucidation of prostate cancer pharmacogenomics have enhanced studies into the impact of germline genetic changes on treatment, in addition to evaluating related genomic alterations and biomarkers in prostate tumor tissues. Currently, Abiraterone (Abi) is used as one of the therapeutic options for PC. In this article, germline variants that have been associated with responses to Abi in patients with advanced PC are summarized. These include biomarker genes such as CYP17A1, AR-V7, HSD3B1, SLCO2B1, SULT1E1, and SRD5A2 that are involved in homologous recombination, as well as in gene expression mutations in important signaling pathways, such as WNT and Abi metabolic pathways.

Keywords: Genetic polymorphisms, abiraterone, prostate cancer, androgen receptor, prognostic

Introduction

Abiraterone (Abi), the prodrug Abi acetate (AA), when combined with prednisone and administered orally, is an effective therapeutic option for metastatic castration-resistant prostate cancer (mCRPC) and metastatic castration-sensitive prostate cancer (mCSPC) [1].

In April 2011, the FDA approved Abi, an androgen synthesis inhibitor, in combination with low-dose prednisone for mCRPC patients that had previously received docetaxel containing chemotherapy. This approval was based on the findings of a phase 3, randomized, placebo-controlled trial (COU-AA-301) in male mCRPC patients that were previously treated with docetaxel. This trial reported that median survival time was 15.8 months in the abiraterone group and 11.2 months in the placebo group (HR, 0.74; 95% CI, 0.64-0.86; P < 0.0001). Moreover, the radiologic progression time, PSA decrease and pain relief were also improved [2-4].

The FDA approved the combination of Abi and prednisone after docetaxel on December 10th, 2012. This approval was based on a randomized phase 3 trial of COU-AA--302 in asymptomatic or minimally symptomatic mCRPC patients, with Abi and prednisone vs prednisone alone. After treatment, the primary endpoint of radiological progression free survival in the combination group increased from 8.3 months to 16.5 months (HR, 0.53; P < 0.001). The median follow-up time was 49.2 months (34.7 months vs 30.3 months; HR, 0.81; 95% CI, 0.70-0.93; P = 0.003) [5].

In February 2018, the FDA approved the combination of Abi and prednisone as a therapeutic option for metastatic prostate cancer. This approval was based on two randomized phase 3 clinical trials of abiraterone and low-
dose prednisone combined with ADT. Compared to ADT alone, the combination group exhibited improved OS outcomes in newly diagnosed patients with metastatic prostate cancer or high-risk or lymph node positive disease (STAMPEDE and LATITUDE) [6, 7].

The adverse events of Abi and prednisone are higher, but generally lighter. These effects are mainly associated with mineralocorticoid excess, hormonal effects and hepatotoxicity. The most common adverse reactions (>5%) were: fatigue (39%); back or joint discomfort (28%-32%); peripheral edema (28%); diarrhea, nausea or constipation (22%); hypokalemia (17%); and hypophosphatemia (24%). The most common adverse drug reactions leading to drug withdrawal were elevated aspartate aminotransferase and/or alanine aminotransferase levels (11%-12%) and heart disease (19%, 6%) [2, 3]. Patient reported outcomes improved with abiraterone treatments, with improvements in pain intensity progression, fatigue, decreased function, prostate cancer-related symptoms, and overall health-related QOL [6, 7].

Despite the demonstrated benefits of Abi, only a small portion of CRPC male patients responded to the therapy. Compared to standard treatment, median progression-free survival (mPFS) outcome from Abi therapy is minor, at less than 6 months. Moreover, nearly 30% of the patients that used Abi developed primary resistance [8]. Although the mechanisms of resistance to Abi have not been fully established, it has been postulated that they are associated with upregulated systemic and intratumoral androgen biosynthesis [9]. This resistance could also be due to the synthesis of more dihydro-testosterone and testosterone from weak adrenal androgens (i.e., dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS)) by the CRPC cells, or make a new start from cholesterol, react to chronic exposure to an environment of low-testosterone [10, 11]. Recently, studies have focused on the effects of germline polymorphisms in androgen biosynthesis, transport, and metabolism-related genes that may influence Abi responses and survival. These polymorphisms include gene mutations of androgen receptors (ARs) and amplification/overexpression, AR splice variants, pathway changes that intersect with AR signals, glucocorticoid receptor overexpression, neuroendocrine differentiation, immune system dysregulation and so on [8]. Studies are evaluating potential biomarkers that can predict therapeutic effects to distinguish among different patients by elucidating on the relationships between candidate gene polymorphisms and clinical outcomes during PC therapy. This could be important in informing individualized Abi treatment.

Many candidate genes involved in metabolism and androgen actions of Abi pathways have been summarized in several reviews. In 2015, Samanta Salvi et al. [12] provided a summary of studies in which the possible roles of genetic variants were clinically investigated based on their predictive significance in gene polymorphisms, prognosis and pathogenesis of prostate tumors. With the elucidation of prostate cancer pharmacogenomics, studies should focus on evaluating the impact of germ-line changes on therapy, in addition to evaluating related genomic alterations and biomarkers in prostate tumor tissues [13, 14]. Eric Johnson et al. [14] summarized the germ-line variants that are associated with therapeutic responses in advanced PC men. With increasing clinical administration of Abi, efforts are aimed at optimizing drug sequencing with a focus on personalizing therapy. Therefore, there is a need to incorporate germline pharmacogenomics into routine clinical use. Currently, reviews on candidate genetic variants of Abi have not been published, however, due to the importance of Abi in PC treatment, such reviews are necessary. This review elucidates on the current status of candidate genes with a clinical impact (Table 1) and provides a reference for the rational clinical use of Abi.

**Action mechanisms of Abi**

Abi, an androgen receptor drug, blocks androgen synthesis in various pathways, including in the testis, adrenal glands, peripheral tissues, and adrenal tumor cells. It selectively inhibits CYP450 17α-hydroxy/17,20-lyase (CYP17A1), an enzyme involved in androgen biosynthesis. Abi exhibits the same 3β-hydroxyl and δ 5-steroid structure as DHEA and other 3β-hydroxysteroid dehydrogenase (3β-HSD) catalytic substrates. Therefore, it can be metabolized by 3β-HSD while still retaining its properties as a CYP17A1 inhibitor, and gains the ability required for effective androgen biosynthesis to
## Pharmacogenomics of abiraterone

### Table 1. Gene polymorphism-related differences in the outcomes of abiraterone for prostate cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>CHR</th>
<th>Minor Allele</th>
<th>MAF</th>
<th>Sample Size Studied</th>
<th>Population</th>
<th>Effect on the Response</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSD3B1</td>
<td>rs1047303</td>
<td>1</td>
<td>C</td>
<td>0.033</td>
<td>76</td>
<td>Caucasian</td>
<td>Not predictive of response to first-line Abi</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>C</td>
<td>0.033</td>
<td>102</td>
<td>Caucasian</td>
<td>The HSD3B1 (1245C) variant allele is associated with a shorter PFS on ADT in patients with mHSPC</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>C</td>
<td>-</td>
<td>99</td>
<td>Japanese</td>
<td>Distinctly better response to Abi</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>C</td>
<td>-</td>
<td>30</td>
<td>NA</td>
<td>Result in a protein variant with increased steady-state levels</td>
<td>[32]</td>
</tr>
<tr>
<td>SLC02B1</td>
<td>rs1077858</td>
<td>11</td>
<td>G</td>
<td>0.353</td>
<td>58</td>
<td>Caucasian</td>
<td>A higher rate of pathologic minimal residual disease on prostatectomy</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>G</td>
<td>-</td>
<td>21</td>
<td>NA</td>
<td>GG genotype showeded a shorter TTBP and PFS than SNP rs1077858 (AA or GA) allele</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>G</td>
<td>-</td>
<td>322</td>
<td>NA</td>
<td>No significant associations between this SNP and outcomes in mCRPC patients (more line therapy)</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>rs12422149</td>
<td>11</td>
<td>A</td>
<td>0.118</td>
<td>59</td>
<td>Caucasian</td>
<td>Increased abiraterone levels within prostate tissue (first-line mCRPC)</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>A</td>
<td>-</td>
<td>323</td>
<td>NA</td>
<td>Significantly improved median PFS (first-line)</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>rs1789693</td>
<td>11</td>
<td>T</td>
<td>0.372</td>
<td>59</td>
<td>Caucasian</td>
<td>Increased abiraterone levels within prostate tissue</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>T</td>
<td>-</td>
<td>323</td>
<td>NA</td>
<td>No differential association with response (first-line mCRPC)</td>
<td>[40]</td>
</tr>
<tr>
<td>SULT1E1</td>
<td>rs3775777</td>
<td>4</td>
<td>G</td>
<td>0.298</td>
<td>68</td>
<td>Caucasian</td>
<td>Significantly associated with increased time to treatment failure</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>rs4149534</td>
<td></td>
<td>C</td>
<td>0.296</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs10019305</td>
<td></td>
<td>G</td>
<td>0.289</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs3775770</td>
<td></td>
<td>T</td>
<td>0.274</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs4149527</td>
<td></td>
<td>T</td>
<td>0.278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs3775768</td>
<td></td>
<td>T</td>
<td>0.271</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs1789777</td>
<td></td>
<td>G</td>
<td>0.298</td>
<td>68</td>
<td>Caucasian</td>
<td>Significantly associated with TTF on AA therapy</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>rs4149534</td>
<td></td>
<td>C</td>
<td>0.296</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs10019305</td>
<td></td>
<td>G</td>
<td>0.289</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs10019305</td>
<td></td>
<td>G</td>
<td>-</td>
<td>322</td>
<td>NA</td>
<td>No significant associations between the evaluated SNP and outcomes in mCRPC patients (more line therapy)</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>rs4149534</td>
<td></td>
<td>C</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs3775777</td>
<td></td>
<td>T</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP17A1</td>
<td>rs2486758</td>
<td>10</td>
<td>C</td>
<td>0.213</td>
<td>87</td>
<td>NA</td>
<td>Diminished shorter time to biochemical progression and biochemical response</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>C</td>
<td>-</td>
<td>322</td>
<td>NA</td>
<td>Significant association with TCR (more line therapy)</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>rs10883782</td>
<td>10</td>
<td>G</td>
<td>0.160</td>
<td>109</td>
<td>French</td>
<td>Associated with rPFS on AA therapy (mCRPC first-line, CRPC-rPFS on AA)</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td>rs743572</td>
<td>10</td>
<td>G</td>
<td>0.394</td>
<td>64</td>
<td>Caucasian</td>
<td>No significant associations between these polymorphisms and clinical outcome</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td>rs10883783</td>
<td></td>
<td>A</td>
<td>0.298</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs17119100</td>
<td></td>
<td>T</td>
<td>0.102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs284849</td>
<td></td>
<td>T</td>
<td>0.177</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP17A1</td>
<td>copy number variations</td>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>NA</td>
<td>Associated with the prognosis of mCRPC patients treated with Abi</td>
<td>[53]</td>
</tr>
<tr>
<td>AKR1C3</td>
<td>Over expression</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>117</td>
<td>Chinese</td>
<td>CRPC-Resistance to abiraterone acetate</td>
<td>[73]</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>rs523349</td>
<td>2</td>
<td>C</td>
<td>0.446</td>
<td>86</td>
<td>Japanese</td>
<td>A worse prognosis in metastatic prostate cancer men for primary ADT</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>rs2300700</td>
<td>2</td>
<td>A</td>
<td>0.459</td>
<td>322</td>
<td>Spanish</td>
<td>No significant associations between the SNP and outcomes in mCRPC patients (more line therapy 66)</td>
<td>[32]</td>
</tr>
<tr>
<td>SRD5A1</td>
<td>rs3822430</td>
<td>5</td>
<td>G</td>
<td>0.379</td>
<td>322</td>
<td>Spanish</td>
<td>Showed a significant association with OS</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>rs3736316</td>
<td>5</td>
<td>A</td>
<td>0.399</td>
<td>322</td>
<td>Spanish</td>
<td>Showed a significant association with OS</td>
<td>[32]</td>
</tr>
<tr>
<td>GNRH2</td>
<td>rs6051545</td>
<td>20</td>
<td>T</td>
<td>0.417</td>
<td>80</td>
<td>Japanese</td>
<td>Higher serum testosterone</td>
<td>[78]</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP/Function</th>
<th>Population</th>
<th>Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>[2105T&gt;A (p.L702H)]</td>
<td>X</td>
<td>37</td>
<td>Caucasian Resistance to abiraterone</td>
</tr>
<tr>
<td>AR</td>
<td>[2632A&gt;G (p.T878A)]</td>
<td>X</td>
<td>37</td>
<td>Caucasian Resistance to Abi</td>
</tr>
<tr>
<td>AR-V7</td>
<td>X</td>
<td>31</td>
<td>Caucasian Positive patients had lower PSA response rates than negative</td>
<td></td>
</tr>
<tr>
<td>AR-V9</td>
<td>X</td>
<td>12</td>
<td>NA</td>
<td>ARV9 expression in metastases related to initial resistance to AA/P</td>
</tr>
<tr>
<td>AR gene amplification</td>
<td>X</td>
<td>12</td>
<td>NA</td>
<td>AA drug resistance (shorter mPSA-PFS and mrPFS)</td>
</tr>
<tr>
<td>SMAD3</td>
<td>upregulated</td>
<td>15</td>
<td>18</td>
<td>NA Drug-resistant</td>
</tr>
<tr>
<td>CCND1</td>
<td>signaling was enriched</td>
<td>11</td>
<td>18</td>
<td>NA Drug-resistant</td>
</tr>
<tr>
<td>DKK4, SFRP2, LRP6</td>
<td>-</td>
<td>8, 4, 12</td>
<td>92</td>
<td>NA WNT pathway activation resistance in mCRPC</td>
</tr>
<tr>
<td>SPOP/CHDI</td>
<td>Mutations/loss</td>
<td>17</td>
<td>89</td>
<td>N A higher response rate to Abi</td>
</tr>
<tr>
<td>FOLH1, KLK3, NPY</td>
<td>negative</td>
<td>11/19/7</td>
<td>50</td>
<td>NA Patients with biomarker-negative platelets had the best outcome. FOLH1 and NPY provided independent predictive information in PFS. KLK2, KLK3, and FOLH1 were associated with short OS</td>
</tr>
<tr>
<td>TSPYL1</td>
<td>rs3828743</td>
<td>6</td>
<td>A</td>
<td>87</td>
</tr>
<tr>
<td>UGT1A4</td>
<td></td>
<td>2</td>
<td>-</td>
<td>5</td>
</tr>
</tbody>
</table>

Pharmacogenomics of abiraterone

act as an AR antagonist and inhibitors of others enzyme. In the past few years, Abi associated metabolites such as 5α-Abi and D4-Abi (D4A), which exhibit significant pharmacological activities, have been shown to be formed by steroidogenic enzymes [15]. 3β-HSD converts Abi to D4A first, which antagonizes the AR while Abi blocks CYP17A1 and steroid-5α-reductase (Figure 1) [16]. Then, D4A is irreversibly converted to 3-keto-5β-Abi or 3-keto-5α-Abi. Both metabolites are then converted to their 3β-OH and 3α-OH derivatives. In total, six downstream D4A metabolites are formed (Figure 2). 5α-Abi is directly metabolized to D4A, with both acting as androgen receptor agonists. However, the 5β-Abi metabolite is not active [15].

Genetic testing

A series of genomic and other molecular analyses have been performed on tumor samples to inform therapeutic decisions by identifying known predictive markers for improving the diagnosis and treatment of PC. To elucidate on the molecular pathological mechanisms in tumor tissues, invasive procedures are often required, which are not always feasible, and continuous monitoring of tumor genotypes is not possible. Currently, cfDNA and CTCs are used to evaluate genetic and epigenetic changes using the NGS of complete exome DNA to establish the transcribed coding and non-coding RNA profiles [17-19]. Matti Annala et al. [19] reported the relative influence of frequent cir-
Pharmacogenomics of abiraterone

Calculating tumor DNA modifications on patient responses to the most extensively used therapeutic options (such as enzalutamide and Abi) for advanced prostate cancer. They used serum samples obtained from a phase II trial, set up genomic drivers of resistance to first line AR treatment in mCRPC and evaluated the possible minimally invasive biomarkers. Studies have reported the potential prognostic values of CTC and AR markers [20-23]. Therefore, development of non-invasive liquid biopsy markers to elucidate on tissue-based information is still a priority, and CTC-based AR-V7 expression is the first such marker that can accurately predict ARSI responses in mCRPC individuals [17].

Polymorphisms associated with abi responses

HSD3B1

The enzyme 3β-HSD1, which catalyzes adrenal androgen precursors into dihydrotestosterone (DHT) is encoded by the HSD3B1 gene. However, due to an amino acid change (p.367T>N) or a missense SNP (rs1047303, NM_000862.3:c.1100C>A) in exon 4 of the HSD3B1 gene, the 3β-HSD1 protein is resistant to ubiquitination and degradation. This results in the accumulation of enzymes, increased intracellular conversion of DHT precursors to DHT and associated progression to CRPC [24]. DHT synthesis is enhanced by variant HSD3B1 (1245C) alleles which predict metastatic disease resistance to ADT and biochemical recurrence after prostate cancer resection. Patients with HSD3B1 (1245C) allele mutations have significantly worse prognostic outcomes after ADT than those without [25], indicating that the HSD3B1 variant status is correlated with shortened ADT response time.

Neeraj Agarwal et al. [26] reported that 10% of males with homozygous HSD3B1 (1245C) mutant alleles have suboptimal responses to ADT alone. These patients may benefit more from a prior therapy of docetaxel or from par-

Figure 2. Genesis of 5α- and 5β-reduced Abi metabolites in patients treated with Abi. The structurally similar conversion from abiraterone to D4A results in the reduction of D4A5α- and 5β at C5, with a total of six additional abiraterone metabolites. D4A: Δ4-abiraterone; 3βHSD: 3β-hydroxysteroid dehydrogenase; 3αHSD: 3α-hydroxysteroid dehydrogenase.
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icipating in prior deeper androgen blockade trials using novel androgen signaling inhibitors. This could have occurred because of the ability of Abi metabolites to act as androgen signaling agonists (3-keto-5α-Abi) and antagonists (D4A) at the same time [27]. Formerly, inheritance of the HSD3B1 variant had been associated with extended responses of non-steroidal drugs to CYP17A1 inhibition, further implying increased tumor dependence on external androgens in males with HSD3B1 mutation [28].

A study [29] involving 76 mCRPC men treated with AA tested the hypothesis that the HSD3B1 (1245C) variant forecasts clinical responses to treatment and can inform on individualized therapy for patients with advanced PC. It was found that the HSD3B1 (1245C) variant did not predict the response of patients using Abi as initial treatment. This outcome could be because Abi metabolites can act as agonists (3-keto-5α-Abi) and at the same time, as antagonists (D4A) during androgen signaling. HSD3B1 (1245C) synthesis predicts faster clinical resistance and sensitivity to extra-adrenal androgen synthesis inhibition [30]. Therefore, HSD3B1 (1245C) looks like to limit a subfraction of patients who benefit from blocking androgens of extragonadal.

Masaki Shiota et al. [25] evaluated the relationships between HSD3B1 genotypes, clinical consequences and clinic-pathological parameters such as PFS, tFFS, OS and PSA responses in 203 Japanese men. A total of 104 men were allocated to the primary ADT cohort, while 99 men were allocated to the Abi group, with most patients in each cohort having metastatic disease. They reported that the prognosis of HSD3B1 mutation carriers was worse in the ADT group, involving 104 mHSPC patients. However, the 99 mCRPC patients with the HSD3B1 variant showed better clinical responses to Abi therapy. Therefore, the HSD3B1 genotype is a potential biomarker for ADT and Abi. It is recommended to apply Abi and ADT in advanced mHSPC patients.

In contrast, a study [31] involving mCRPC patients receiving Abi as first-, second- or third-line therapeutic options showed that there were no significant associations between HSD3B1 (rs1047303) and clinical outcomes. Therefore, they determined whether the inheritance of HSD3B1 (1245C) is associated with increased 3-keto-5α-Abi synthesis [32]. They found that individuals who inherited 0, 1, 2 copies of HSD3B1 (1245C) have a gradual increase in normalized 3-keto-5α-Abi. These patients were more likely to benefit by inhibiting CYP17A1, however, Abi benefits were partially offset by elevated 3-keto-5α-Abi levels.

Even Although the HSD3B1 (1245C) allele increases the rate by which adrenal androgen precursors are converted to DHT, AR antagonists compete with intratumoral androgens and may weaken the effect of the mutant allele. Therefore, the high exposure rate to early ADT and the frequent use of AR antagonists during ADT rescue treatments may change the genotypic effect on composite TTP and OS.

Recently, large individual differences in the metabolic ratios of Δ4A/Abi (CV = 140%) when 3β-HSD1 transforms Abi into Δ4A have been reported [33]. An increase in the Abi to Δ4A ratio may predict the heterozygous or homozygous variant of the patient (1245C), and is also associate with individual differences. In addition, inheritance of HSD3B1 (1245C) variants is associated with elevated AR agonist 5-α-Abi levels. These results suggest that plasma exposure to Abi affects pharmacodynamic activities in mCRPC patients treated with Abi than with Δ4A. Furthermore, Δ4A level or ratio may be a substitute of endogenous 3β-HSD1 activity, which partly depends on HSD3B1 genotype inherit [34].

There are divergent opinions on whether HSD3B1 gene polymorphisms can be used as biomarkers for AA to treat prostate cancer. Some studies [25, 26] have confirmed that therapeutic outcomes are predictive when AA is used as a first-line therapeutic option for CSPC. However, for men exposed to ADT from non-steroidal androgen drugs, HSD3B1 cannot predict clinical outcomes, possibly because HSD3B1 may have been affected by previous ADT treatments [27]. Therefore, further studies are needed to evaluate the impact of this gene in patients with different stages of prostate cancer.

SLCO2B1

Solute carrier organic anion transporter family member 2B1 (SLCO2B1) is involved in the transport of hormones such as testosterone.
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and dehydroepiandrosterone sulfate (DHEAS) as well as drugs such as AA [35]. Therefore, germline variations in SLC02B1 can alter therapeutic responses to therapies targeting the androgen axis. This outcome has been observed in multiple studies [36-38] in which SLC02B1 SNPs have been associated with resistance to ADT. The organic anion-transporting polypeptides (OATPs) transport a variety of compounds, including adrenal androgens, which are encoded by SLCO genes.

Elahe A Mostaghel et al. [39] reported that SLC02B1, rs12422149 and rs1789693 SNPs are associated with elevated Abi levels within the prostate tissue and a higher rate of pathologic minimal residual disease on prostatectomy.

A study [40] evaluated the predictive value of SLC02B1 germline variants (rs1789693 and rs12422149) on PFS in mCRPC men administered with first-line Abi. Men heterozygous for the rs12422149 variant allele had a significantly improved median PFS compared to those homozygous for wild-type rs12422149 allele. There were no differential associations in responses to treatment with Abi for patients with the rs1789693 genotype. Germline variant alleles of SLC02B1 (rs12422149) are frequent and are potential predictors for improved responses to first-line Abi in mCRPC male patients.

Silvana Giacinti et al. [41] hypothesized that germline variants of the androgen transporter gene (SLCO2B1) may influence responses to Abi in mCRPC male patients by altering the stock ability of adrenal precursors to prostate cancer cells. Three single nucleotide polymorphisms (SNPs), intronic SNPs (rs1789693 and rs1077858) and an exonic SNP (rs12422149), were genotyped in 21 mCRPC male patients who had been treated with Abi. Patients carrying the SLC02B1 rs1077858 risk genotype (GG) showed a shorter PFS and TTBP than patients with the primary AA or GA allele. Therefore, SLC02B1 genetic variants may be pharmacogenomic determinants of resistance to Abi in mCRPC. This phenomenon has been elucidated [42]. It was reported that there are clear differences in SLC0 expression between Gleason score 4 and 3 tumors, ADT-treated and untreated tissues as well as between PCa and NP samples. Although the study involved a small sample, these results showed that steroid ADT uptake and response may be influenced by baseline and changes in ADT-induced PCa OATP expression, as well as uptake and response of drugs transport by OATP-mediated such as Abi and docetaxel, which are now commonly used in combination with ADT in mCSPC patients.

Costantine Albany et al. [43] reported that SLC02B1, KIF3C CYP19A, and ESR1 polymorphisms are significantly associated with PFS during Abi therapy (P<0.025; q-value < 0.69). This result showed the importance of gene polymorphisms in individualized treatment with Abi. There is a need to determine whether correlations of more than one polymorphism with longer TTP and PFS is a predictor for better responses to treatment.

SULT1E1

Estrogen sulfotransferase (SULT1E1) belongs to the cytosolic sulfotransferase superfamily, which are Phase II drug-metabolizing enzymes. They mediate sulfate conjugation that is important in xenobiotic detoxification and regulate multiple signaling molecules [44]. In the human reproductive tissue, SULT1E1 catalyzes the sulfation of estrogenic compounds [45]. Estrogen has a key role in PC pathogenesis and outcomes [46]. AA inhibition of DHEA sulfonation has been confirmed in enzymatic cultures containing human liver or intestine tissue cytosol or recombinant human SULT2A1, SULT2B1b or SULT1E1 enzymes [47].

A study [48] evaluated the correlation between time to treatment failure with Abi and 832 SNPs in 61 candidate androgen pathway genes from 68 mCRPC patients. After correcting for multiple testing and controlling for other clinical variables, 6 SNPs (rs3775777, rs4149534, rs10019305, rs3775770, rs4149527, and rs3775768) in one gene, SULT1E1, were significantly correlated with increased time of treatment failure. Another study [49] arrived at a similar conclusion, where estrogen sulfotransferase genes, rs3775777, rs4149534 in SULT1E1 were significantly correlated with TTF in Abi treatment and may act as prognostic markers for efficacy upon treatment with Abi in Caucasian mCRPC male patients. These SNPs are potential predictive markers for Abi and should be validated in a larger cohort.
CYP17A1

The human CYP17A1 gene is localized on chromosome 10q24.3, spans 6.6 kb and contains eight exons and seven introns. In adrenals and gonads, an identical 2.1 kb mRNA is transcribed from this gene [50]. In the adrenals, the expression levels of CYP17A1 are regulated by the adrenocorticotropic hormone (ACTH), and by gonadotropic hormone in the testes and ovaries. Due to its activity on 17-hydroxylase and 17,20-lyase, which play vital roles in hormonal production pathways, the CYP17A1 gene is very important in the production of androgens and glucocorticoids [51].

As a CYP17A1 inhibitor, alterations in CYP17A1 have been implicated in resistance to Abi [52]. A study [53] showed that CYP17A1 copy number variations affects the prognosis of mCRPC patients treated with Abi.

Moritz Binder et al. [54] evaluated the associations between four CYP17A1 tag SNPs and responses to Abi in 87 male mCRPC patients. Four SNPs (rs743572, rs4919685, rs2486758, and rs17115100) provided a 100% coverage of CYP17A1 common genetic variants (minor allele frequency 0.05). A single SNP (rs2486758) was confirmed to be associated with diminished shorter time to biochemical progression and biochemical responses.

Nine SNPs of 6 candidate genes have been previously analyzed [32]. They include CYP17A1 (rs2486758), SRD5A1 (rs3822430 and rs3736316), SRD5A2 (rs2300700), SLC02B1 (rs1077858), SULT1E1 (rs10019305, rs377577 and rs4149rs104) and HSD3B1 (rs1047303). A single SNP of CYP17A1 (rs2486758) was significantly correlated with TCR (time to castration resistance). There were no significant associations between most of the evaluated SNPs and outcomes in Abi treated mCRPC male patients. Unlike other studies, patients involved in this study received Abi as the first-, second- or third-line therapeutic option.

The ABIGENE study [55], a multicentric prospective non-randomized pharmacogenetic study, evaluated mCRPC patients treated with AA+prednisone as first-line therapy. Based on the PCWG2 criteria, they found that the association between 13 SNPs in genes (CYP17A1, SLC02B1 and SLC02B3) are associated with Abi pharmacology and radiographic progression-free survival (rPFS). During Abi treatment, SNP CYP17A1 (rs10883782) was associated with rPFS. Statistical analyses did not reveal significant associations between rs10883783, rs743572, rs284849 and rs17115100 polymorphisms in CYP17A1 and prognosis. However, patients with the TT genotype of rs10883783 exhibited longer PFS than patients with the AA or TA genotype by 3-months [56].

In summary, single SNP (rs2486758) in CYP17A1 was significantly correlated with poor clinical outcomes and resistance to Abi treatment. More studies will transform these conclusions into decision-making indicators for clinical treatment.

AKR1C3

Aldo-Keto Reductase Family 1 Member C3 (AKR1C3) is a protein-coding gene. The diseases associated with AKR1C3 include prostate disease and endometrial cancer. Annotations in Gene Ontology (GO) related to this gene include the activity of oxidoreductase and aldo-keto reductase (NADP). AKR1C3 plays a key role in all DHT pathways, including catalysis of conversions from Δ4-androstene-3,17-dione (Δ4-AD) to T, 5-Adione to DHT, and DHEA to 5-Adiol [57].

Overall gene expression analyses revealed that the steroid biosynthetic pathway is activated in prostate cancer cells resistant to Abi [58]. One of the key steroid-like gene enzymes, AKR1C3, has been found to be significantly elevated in Abi-resistant cells. In addition, AKR1C3 is highly expressed in metastatic and recurrent prostate cancer. Moreover, compared to parental cells, androgen precursors, such as cholesterol, dehydroepiandrosterone and progesterone, as well as androgens, are highly upregulated in Abi-resistant prostate cancer cells. The overexpression of AKR1C3 confers resistance to Abi. AKR1C3 expression has been observed in prostate cancer cell samples grown in androgen-depleted media [59], in xenografts from castrate mice [60-62], in tumor samples of patients with soft-tissue metastases [10] and in nine clinical studies [10, 18, 59, 63-67]. These results suggest that AKR1C3 activation is a critical resistance mechanism associated with Abi resistance.
AKR1C3 is also associated with the backdoor pathway, where it converts androsterone to 3α-diol [67-69]. AKR1C3 expression is up-regulated by ADT and is inhibited by androgens, and its overexpression is part of the mechanisms associated with Abi resistance [61]. The TMPRSS2-ERG fusion protein binds the AKR1C3 promoter to enhance the expression of AKR1C3. The pre-pass mechanism has been proposed, in which, when the tumor starts to synthesize more T and DHT, TMPRSS2-ERG expression is elevated, which replaces the AR in the AKR1C3 promoter, thereby enhancing intratumoral androgen biosynthesis [66]. Tamae D. et al. [70] reported that one of the mechanisms involved in Abi resistance is that DHEA-SO4 residues and AKR1C3 overexpression after CYP17 inhibition form a storm for AA drug resistance.

Some studies [71, 72] have reported that AKR1C3 detection of prostate re-Bx in mCRPC tissue is associated with early Abi resistance. That is, AKR1C3 significantly shortens mPSA PFS and mrPFS. The expression of AKR1C3 is not correlated with PSA response and OS. These findings inform clinical decisions on the best personalized treatment for mCRPC patients, and help clinicians predict Abi effectiveness, therefore, it is recommended to routinely describe it in the pathology report.

Studies [73, 74] have also evaluated the effects of AKR1C3 on the therapeutic effect of corticosteroid conversion in predicting mCRPC patients receiving Abi treatment. One study showed that AKR1C3 expression by mCRPC in prostate re-Bx tissue is associated with the shortening of PSA-PFS caused by the conversion of glucocorticoid from prednisone to dexamethasone. These conclusions have a certain reference value for mCRPC patients, especially for the individualized choice of corticosteroid conversion therapy.

In summary, activation of AKR1C3 enhances androgen secretion, which is a key mechanism for Abi resistance. Therefore, targeting AKR1C3 activation is a potential treatment strategy for patients with metastatic prostate cancer who are resistant to Abi and corticosteroid conversion therapies.

SRD5A

Genetic variations in genes associated with androgen production pathways such as GNRH2 (rs6051545) and SRD5A2 (rs523349) are related to serum testosterone levels and prognosis during ADT [75-77]. In addition, SRD5A2 gene polymorphism is correlated with the prognosis of metastatic PC after primary ADT. SRD5A2 encodes 5α-reductase 2, which can convert testosterone to 10 times stronger DHT [75]. M Shiota et al. determined whether serum testosterone concentration or body mass index (BMI) in patients with metastatic PC and primary ADT is correlated with prognosis. In addition, the association between serum testosterone levels and SRD5A2 polymorphism was examined during ADT. The CC SRD5A2 (RS523349) allele encodes a less active 5α-reductase, which is associated with decreased serum testosterone levels in the course of ADT. These findings suggest that significant inhibition of SERUM testosterone by ADT is correlated with SRD5A2 polymorphism [75].

It has been reported [76] that a greater active 5α-reductase variant encoded by the GG allele of SRD5A2 (rs5233499) is associated with poor clinical outcomes in patients with metastatic PC treated with essential ADT. Moreover, patients with the CC allele, which encodes the less active 5α-reductase, have lower plasma testosterone concentrations and better clinical outcomes upon ADT therapy. It is advised that distinction of blood testosterone levels during ADT treatment might also mediate the prognostic impact of SRD5A2 polymorphism. It has not been established whether plasma testosterone concentrations in the course of ADT therapy is an independent prognostic for SRD5A2.

GNRH2

Gonadotrophin-releasing hormone (GnRH) is a decapeptide that is synthesized by the hypothalamus. Two subtypes of GnRH, GnRH1 and GNRH2, are expressed in the trophoblast and syncytiotrophoblast of human placenta, respectively. The GNRH2 gene is located on chromosome 20p13 and has 70% homology with the GnRH1 gene, and consists of 4 exons [77].

A Japanese study [78] measured serum testosterone levels of 80 mCRPC patients on ADT treatment. Compared to the CC allele, the CT/TT and CT alleles in the GNRH2 gene (rs6051545) were associated with elevated plasma testosterone concentrations. During ADT treat-
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Abnormal AR gene mutations are rare. However, in rapid autopsy diagnosed metastatic tumors before hormonal therapy, up to 60% of patients were found to have these mutations [79]. Two AR point mutations, 2632A>G and 2105T>A, are associated with Abi resistance and are activated by progesterone or prednisone former, respectively [80-83]. Findings from related biomarker studies revealed that the AR gene status in plasma DNA is correlated with poor prognosis of CRPC patients on Abi.

Androgen-receptor splice variant (ARV)

The ARV level is associated with PC process, and there is a significant elevation in ARV expression during ADT [81-87]. This may be attributed to the activation of AR in the ligand resulting in the absence of an AR clipping variant of the ligand binding domain (LBD) as a transcription factor to maintain continuous activity in a ligand non-dependent manner [88]. AR-V7 and ARV-567 are the most commonly expressed variants that are associated with PC progression during ADT [89]. Abi therapy is correlated with an increased truncated variant expression, and ARV expression can mediate resistance to treatments targeting FL AR and mCRPC cell line in CRPC xenografts [90].

AR-V7: AR-V7, a special AR-V, develops from contiguous splicing of AR exons 1, 2, and 3 and cryptic exon 3 [91]. Due to selective splicing of 30 terminal cryptic exons, AR-Vs lacks the full-length AR COOH terminal LBD [92]. These 30 terminal cryptic exons encode short carboxy-terminal extensions. The expression levels of exon CE3 as the 30-terminal exon of AR-V7 has been used for RT-PCR, in RNA sequencing (RNA-seq) and in in situ hybridization (ISH) to detect the mRNA expression levels of AR-V7 in all kinds of biological samples from CRPC patients [93-102]. Positivity of AR-V7 expression in CTCs is correlated with resistance to Abi, but not to taxane therapy [17, 94]. AR-V7 is associated with CRPC pathogenesis, and its prognostic value in CRPC should be further elucidated. In CRPC patients treated with androgen receptor signaling (ARS) inhibitors, AR-V7 positive is associated with poor PSA response and PFS prognosis. However, it does not have an effect on the OS of chemotherapy patients. Even though AR-V7 detection based on circulating tumor cells (CTC) has been shown to predict patient’s responses to second-generation androgen receptor therapy, AR-V7 is rarely expressed in mCRPC patients, suggesting that other factors mediate resistance.

A study [103] reported that PSA response rates of AR-V7-positive patients to androgen receptor signal suppression therapy was significantly lower than that of AR-V7-negative patients. The OR of PSA response in AR-V7-positive patients has been found to be 0.07 (95% CI, 0.02-0.35; P = 0.0010) in patients treated with Abi. In global case series or in male patients allocated into three groups based on basic PSA levels, when CTC negative to CTC positive/AR-V7 negative to CTC positive/AR-V7 positive, all approved treatment results deteriorated. Pierangela Sepe et al. [104] reported that when individualized biomarker-driven therapy is extended to all patients, priority should be given to combining the predictive effect of CTC status with AR-V7 detection.

A study [17] involving Abi-treated CRPC patients reported that AR-V7 was positive in CTCs in 31 patients, and that these patients had low PSA response rates than patients without AR-V7 expression. The median clinical or radiographic PFS in patients without AR-V7 expression was longer than in the AR-V7-positive group in men with Abi. In addition, 9-15% of mCRPC patients were positive for AR-V7 expression at initial treatment, and AR-V7 exhibited an increasing trend during Abi treatment, supporting the hypothesis that AR-V7 is associated with both intrinsic and acquired resistance of patients to Abi [105, 106].

These studies imply that AR-V7 is a potential predictive biomarker in precision therapy. Inhibiting the transcriptional activity of AR-V7 and reducing the recruitment of AR-V7 to PSA promoters can be a vital therapeutic strategy, and
may also be an advantageous way for overcoming Abi resistance [107].

Sumanta Kumar Pal et al. [108] reported contrasting findings to those of previous CRPC studies. They did not report significant differences in AR-V7 levels between drug resistance and drug-sensitized patients and neither did they report that high AR-V7 baseline levels imply a weak response to Abi. All four patients with elevated AR-V7 baseline levels initially responded to Abi, even though they progressed to resistance within one year of initial Abi.

Even though evidence suggests that AR-V7 expression levels cannot be used as predictive markers for targeted AR therapy, studies [109, 110] have reported that this is not always exact and individuals with positive AR-V7 expression may still benefit from Abi. In addition, this suggests that other mechanisms other than AR splicing variant expression may lead to resistance to these drugs.

AR-V9: Abi acetate can be used as a target for transcriptional reactivation of AR in some patients, and in most cases, the transcriptional activity of AR persists [110]. These two AR variants, AR-V9 and AR-V7, have a common 30-terminal recessive exon, which predisposes AR-V9 to experimental manipulations that were previously thought to be AR-V7 specific. Since AR-V9 promotes the growth of prostate cancer cells that do not rely on ligands, elevated mRNA expression levels of AR-V9 in CRPC metastases is a predictor of initial resistance to Abi. Therefore, AR-V9 may be an important part of CRPC resistance. A study [110] assessing mCRPC individuals begin with pre-chemotherapy Abi+P accepted biopsies of metastatic site before and after 12 weeks-therapy. Compound progression included PSA, RECIST, bone scan and symptoms (by PCWG2), which were evaluated at 12 weeks (primary endpoint). The associations between resistance at 12 weeks of Abi therapy and these parameters, including mRNA expression of pre-AA/P ARFL (full-length AR), AR-V3, AR-V7, AR-V9, AR-V23, AR-V45, four cell cycle division genes, PSA/testosterone levels at initial diagnosis, chromogranin A (CHGA) along with Gleason score (GS), tumor volume and time from start of hormonal therapy to mCRPC stage were evaluated by logistic regression models. It was found that elevated AR-V9 mRNA expression levels in metastases is correlated with early resistance to AA+ prednisone. This finding should be validated in similar studies.

Androgen receptor amplifications

Even though findings from AR amplification testing were not superior to standard prognostic biomarkers, the LBD truncated AR gene is rearranged in patients with primary drug resistance. These studies confirmed the driver genes for resistance to first-line AR treatment in patients of mCRPC, and identified the potential biomarkers for minimally invasive testing [19].

Signaling pathway

TGFβ/SMAD3 and CCND1

From the RNA-seq findings of CTCs, classic mutations correlated with CRPC and new mutations were identified, including in AR ligand binding domains that help escape AR-targeted drugs. Pathway evaluations of differentially regulated genes [111] revealed that cyclin D1 (CCND1) and transforming growth factor β (TGFβ) signaling pathways are substantially upregulated in drug resistance. These findings indicate that Abi-sensitive and Abi-resistant states represented by RNA-seq of CTCs are potential resistant mechanisms. Moreover, CCND1 signaling and TGFβ/SMAD family member 3 (SMAD3) play key roles in driving oncogenic conversion after AR-targeted therapy.

Wnt pathway

The WNT pathway is associated with mCRPC drug resistance [112], and can induce tumor transformation from epithelial to mesenchymal states. Mesenchymal transformed cancer cells stimulate the invasion of adjacent epithelial cancer cells by secreting WNT5B [113].

Manish Kohli et al. [111] reported that activation of the Wnt/catenin pathway is associated with primary AA/P resistance. They also found that Wnt/β-catenin pathway associated genes often have mutations, and the negative regulators of the Wnt pathway (SFRP2, LRP6 and DKK4) are often deleted in non-responders. Gene expression analysis showed that expression levels of cell cycle regulation genes in non-responders increased significantly, and at
the same time, the expression levels of the Wnt/catenin pathway inhibitors decreased significantly. This discovery provides the possibility for establishing predictive biomarkers to regulate target pathways to overcome molecular resistance to Abi.

Some studies have reported that the expression of Wnt transcripts, such as WNT5A and WNT7B, and genes related to classical Wnt signaling, including LEF1 and FZD4 in resistant samples are significantly elevated [96, 108, 112]. However, they did not observe elevated expression levels of non-canonical Wnt pathways such as target “cell division control protein 42 homolog” (CDC42), RAC, or RHOA. Moreover, these non-classical pathways have not yet been shown to be enriched in drug-resistant samples. Therefore, the activation levels and clinical relevance of Wnt pathway in drug-resistant prostate cancer should be further elucidated.

Genome-wide analysis of patients with initial Abi resistance revealed that there is a frequency of variation in the WNT pathway. Therefore, the value of Wnt pathway in Abi resistance should be further evaluated in studies.

**SPOP**

Tumor genome-wide and exome sequencing studies have shown that SPOP is the most commonly mutated gene in primary prostate cancer. It is a substrate of cullin-3 (CUL3) ring box 1 (RBX1) E3 ubiquitin ligase (CRL) complex object recognition subunit [114]. In prostate cancer, SPOP mutations are associated with a structurally labeled substrate binding region known as the region of methylidopa and tumor necrosis factor-related factor (TRAF) homology (MATH) [115-117]. These findings suggest that the pathophysiology originating from SPOP mutations may be mediated by impaired substrate ubiquitination.

SPOP mutations and CHD1 deletions frequently occur in prostate cancer, with lower frequencies reported in CRPC. A study [118] evaluated the key molecular characteristics of mCRPC for CHD1 deficiency/SPOP mutations, and showed that they are associated with a high probability of benefit from Abi therapy. CHD1 deficiency is significantly correlated with SPOP mutations, while ERG re-scheduling is negatively associated with SPOP mutations and CHD1 deficiency, suggesting that these genomic bits have selective roles in prostate cancer progression.

Studies have determined that SPOP mutations appear in the early stages of prostate tumors and are associated with the loss of CHD1, thus defining a subclass of the disease. It has been reported that SPOP mutations are associated with increased androgen receptor (AR) signaling pathways. Therefore, it has been hypothesized that SPOP-mutated prostate cancer is highly sensitive to AR blockade during Abi treatment. It has been reported [119] that this subclass of prostate cancer is very sensitive to Abi’s AR signal blockade, and that most tumors with SPOP mutations/CHD1 deletion respond to it.

A study [119] reported that most of the PTEN in the wild-type background of CHD1 and SPOP in mCRPC of localized prostate cancer was missing, and two patients with both CHD1 and PTEN missing at the same time were reported, indicating that the combination of these two proteins’ basic relationships are not universal. Moreover, this study reported several SPOP mutations including R121P, G148E, E50K, S105F, Q120R, and A187T that were not reported in previous systematic prostate cancer studies.

**Other metabolic pathways**

**TSPYL**

The testis-specific y-encoding-like protein (TSPYL) gene family includes TSPYL1 to TSPYL6. Among them, TSPYL1, 2 and 4 regulate the expression of many CYP genes, such as CYP3A4 and CYP17A1, which encode enzymes that catalyze Abi metabolism and key enzymes for androgen biosynthesis, respectively. In addition, a common SNP of TSPYL1, rs3828743 (G/a) (Pro62Ser), suppresses the ability of TSPYL1 to inhibit the expression of CYP3A4, resulting in a decrease in Abi concentration and an increase in cell proliferation. SNP genotype A is significantly associated with adverse reactions. A prospective clinical trial of 87 mCRPC men administered with Abi acetate/prednisone revealed a significant correlation between poor clinical responses and short PFS. Therefore, as a new CYP gene transcription regulator, the TSPYLs gene affects re-
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responses to drug therapy because genetic changes significantly regulate CYP450 gene transcription [120].

**UGT1A4**

A study [121] showed that Abi and its metabolites undergo glucuronidation in the liver, and different levels of glucuronic acid derivatives are detected in the blood of PC men. UDP-glucuronosyltransferase (UGT)1A4 is a key enzyme. Mutations of this enzyme were shown to affect this metabolic pathway in vitro, suggesting that it may affect the metabolism and function of Abi in patients. These drug compounds inhibit the effects of drugs and steroidal glucuronic acid, and may affect the UGT-related agent metabolism system and the pre-receptor control of androgen metabolism in patients.

**CYP450**

Abi can be extensively metabolized through a variety of pathways, but mainly through the transformation of SULT2A1 to Abi sulfate (M45), and to N-oxide Abi sulfate (M31) by SULT2A1 and CYP3A4 [122, 123]. M31 and M45 are the major metabolites that are not active, and they account for 40% of Abi in blood serum [123]. In vitro studies indicated that Abi is a strong inhibitor of CYP1A2 and CYP2D6 as well as a moderate inhibitor of CYP2C9, CYP2C19, and CYP3A4 [124]. In vitro, Abi sulfate and N-oxide Abi sulfate inhibited OATP1B1, the hepatic uptake transporter [125], which indicates potential interactions between drugs and OATP substrates. However, currently, there is no evidence of drug interactions due to transporter induction or inhibition [125].

**FASN overexpression**

Abnormal regulation of lipid metabolism caused by overexpression of fatty acid synthase (FASN) is an important sign of prostate cancer progression. FASN is a key enzyme for restarting fatty acid synthesis. FASN and AR-FL have been detected in 87% of mCRPC metastases, with AR-V7 being found in 39% of bone metastases, and they were always co-expressed with FASN. FASN/AR-V7 double-positive metastases have been reported in 77% of Abi treatment cases. These findings provide compelling reasons for the use FASN inhibitors in mCRPC, including in those who overexpress AR-V7 [126].

**KLK3, FOLH1, and NPY**

Results [127] from the Abi-treated cohort revealed that detectable biomarkers (FOLH1, KLK3 and NPY) are associated with short PFS. Patients with negative platelet biomarkers have the best clinical outcomes. FOLH1 and NPY as biomarkers have been shown to have independent predictive values in the multivariate analysis of PFS. Three biomarkers (KLK2, KLK3 and FOLH1) are associated with a short OS. Introducing the three biomarkers of KLK3, FOLH1 and NPY in one panel at the same time can predict long-term and short-term responders with a sensitivity of 87% and a specificity of 82%.

**Conclusions**

Approval of Abi for mCRPC has greatly enriched the treatment strategy for PC. However, many germline variants have been shown to affect clinical responses in men with advanced PC to systemic treatment. Associations between germline variants such as HSD3B1, SLCO2B1, SULT1E1, CYP17A1, SRD5A2, AR-V7 and clinical responses to ADT in CSPC have been extensively validated in independent cohorts, but gene mutations in the WNT signaling pathway, SPOP, KLK3, FOLH1, NPY and metabolic pathways are worthy of attention.

Since genetic polymorphisms have been shown to exhibit contradictory effects on the clinical outcomes of Abi in the treatment of PC, larger-scale studies should be performed to evaluate genetic polymorphisms of Abi as biomarkers in clinical practice. The correlation between SNPs and treatment outcomes can be used as prognostic and predictive biomarkers for patient stratification and to distinguish between individualized therapy and follow-up plans. Therefore, studies should aim at establishing a corresponding model to determine the influence of the clinical outcomes of genes that can be applied for clinical, individualized treatment.

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Disclosure of conflict of interest

None.

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